Late Failure in Cadaveric Renal Allografts

SUMMARY.—Sixteen patients with renal cadaveric allografts who have survived for one year or longer are reported. The patients were analyzed from the standpoint of incidence, quantity and course of proteinuria in relation to renal function and the nature of the original disease.

This analysis shows that proteinuria is progressive and is accompanied by a decline in renal function when the original disease is of an immune nature. This was not so in patients with non-immune original disease. These findings suggest that recurrence of original disease plays an important role in late failure of cadaveric renal allografts.

Failure of a cadaveric renal allograft after one year generally has been attributed to chronic rejection[1-4] except in a few instances where recurrent disease has been postulated.[5-7] Analysis of post-transplantation proteinuria in relation to renal function and the nature of the original disease suggests that recurrent disease may be a more important factor in late failure than was previously considered.

Materials and Methods

This study is based on 16 cadaveric renal allografts which functioned for one to nearly five years. Recipients' ages ranged from 12 to 52 years. Eleven were males and five were females. All patients except one underwent bilateral nephrectomies. Several also had splenectomies.

Chronic immunosuppressive therapy consisted of azathioprine (2-3 mg. per kg. body weight daily) and prednisone (15 mg. daily in divided dosage). The graft site was irradiated, using four doses to a total of 600 roentgens during the first 10 postoperative days. Acute rejection was treated by increased steroid dosage and actinomycin C during the periods of crisis. Antilymphocytic globulin was not employed.

The patients were divided into two groups on the basis of the original disease. Twelve patients had primary renal disease of a presumed immune nature (ID group). Diagnosis was based on light microscopy of the resected or biopsied original kidney, the clinical picture and massive proteinuria. The remaining four patients had primary non-immune original disease (NID group). Three of these had polycystic kidney disease and the fourth had hereditary nephritis of Alport's type.

Chronic follow-up care was carried out at least at monthly intervals. Twenty-four-hour urine collections were quantitated for protein by the turbidimetric procedure.[8] Creatinine was determined by the Jaffe reaction as modified for the AutoAnalyzer.[9] Creatinine clearance was calculated on a 24-hour period.

Tissue from the transplanted kidney was obtained in eight patients. In seven, necropsy or transplant nephrectomy provided the material, while in the remaining instances percutaneous needle biopsy was carried out. Unfortunately none of the tissue could be examined by immunofluorescent technique or electron microscopy.

Leukocyte typing and antiglomerular basement membrane antibody studies were not possible.

Results

For present purposes proteinuria has been arbitrarily defined as 0.5 g. or more excretion in 24 hours. Table I demonstrates that the incidence of proteinuria in the ID group rose from 5/12 (42%) at 12 months to 3/3 (100%) at 30 months. In striking contrast, none of the patients in the NID group showed proteinuria as defined at any time during the study period.

Eight patients out of the 12 with original disease of an immune nature have developed proteinuria of 500 mg. or more per day. Table II sets forth in detail the course of proteinuria in these patients. It becomes apparent that once proteinuria appears, it increases in magnitude in time. Six out of the eight patients have reached protein excretion in the nephrotic range (greater than 3.5 g. per day). Of the two who have not, patient CD12 can be discounted because he died of non-renal causes one year later. Patient CD21 has shown a fluctuating degree of proteinuria. It is important to stress that low-grade proteinuria or absence of proteinuria can persist for as long as 18 to 24 months before the development of heavy proteinuria.

Table III relates the proteinuria to the creatinine clearance. It is apparent in the patients with proteinuria in the ID group that the creatinine clearance deteriorates in time. This decline may coincide with the occurrence of heavy proteinuria but in some instances may follow it by many months. The creatinine clearance does not deteriorate in time in patients whose original disease was non-immunological. This is evident in Table IV, which compares the creatinine clearances in the two groups.

Presented at the Annual Meeting of the Royal College of Physicians and Surgeons of Canada, Vancouver, B.C., January 1969.

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Discussion

These observations show that in our series of cadaveric renal allografts, late failure has followed a definite pattern. It has occurred only in patients who had immune original disease and was heralded by proteinuria which was progressive. This is directly opposed to the fate of those cadaveric allografts in patients whose original disease was of a non-immune nature. These patients were free of proteinuria and excellent renal function was maintained.

These results suggest that recurrence of original disease plays a significant role in the outcome of cadaveric renal transplants. Recurrence of the original disease in the transplanted kidney has been demonstrated by others. In a series of 18 isografts where the original disease was glomerulonephritis, 11 patients developed recurrent glomerulonephritis.[5] The onset of recurrent disease ranged from one day to six years after the transplant, averaging two years. Lerner, Glassock and Dixon[10] have described a possible pathogenic mechanism.

If late failure were due to chronic rejection alone, then a division on the basis of the nature of the original disease, as we have shown, would be unlikely, unless individuals with hereditary renal disease have immunological incompetence. The latter has not been demonstrated.

Unfortunately, histological examination of the tissue does not resolve the question. Porter and his colleagues[11, 12] have attributed the glomerular lesions in their combined series to chronic rejection. One of their major reasons for doing so is that, of the 27 patients with "pronounced basement membrane deposits" who were studied, five had non-immunological disease where recurrence could not be a factor. Closer scrutiny of their data challenges this postulation.

TABLE I.—Incidence of post-transplant proteinuria

	ID group			NID group		
No. of months post-transplant	*Total no. of patients*	*No. with proteinuria*	*Per cent with proteinuria*	*Total no. of patients*	*No. with proteinuria*	*Per cent with proteinuria*
4	12	5	42	4	0	0
8	12	5	42	4	0	0
12	12	5	42	4	0	0
18	9	5	55	3	0	0
24	6	5	83	3	0	0
30	3	3	100	2	0	0
36	3	3	100	1	0	0
48	2	2	100	0	0	0

ID and NID are primary renal disease immunological and non-immunological as defined in the text. Proteinuria is defined as urinary excretion of protein of 0.5 g. or more per day. Total number of patients in ID group diminishes with passage of time because insufficient time has elapsed since transplantation, except between 12 and 18 months where two of the deletions result from patient death due to (1) cerebral hemorrhage and (2) transplant failure. Total number of patients in NID group diminishes because insufficient time has elapsed since transplantation except between 30 and 36 months where the deletion resulted from death of a patient due to an acute myocardial infarction.

TABLE II.—Progression of post-transplant proteinuria in ID group

	No. of months post-transplant							
Patient no.	*4*	*8*	*12*	*18*	*24*	*30*	*36*	*48*
CD02	0	0	0	0	0.5	2.1	4.5	5.5
CD03	0.2	0.5	0.3	0.8	0.8	2.1	2.3	3.5
CD11	0.9	1.8	3.5	3.9	3.7	4.3	5.6	x
CD12	0.2	0.4	0.5	d	—	—	—	—
CD15	0.2	0.2	0.2	3.8	4.5	x	x	x
CD17	0.4	0.3	0	0.2	0.1	x	x	x
CD19	0.5	1.4	2.9	2.6	8.0	x	x	x
CD21	2.1	1.1	1.7	1.4	x	x	x	x
CD22	0.4	0.4	0	0.1	x	x	x	x
CD25	0.5	4.6	12.0	f	—	—	—	—
CD28	0.3	0.4	0.3	0.2	x	x	x	x
CD29	0.1	0.3	0	x	x	x	x	x

Proteinuria is expressed in grams of protein excreted in the urine per day.
x Insufficient time elapsed since transplantation.
d Death of the patient without transplant failure.
f Failure of the transplant without death of the patient.

TABLE III.—Creatinine clearance post-transplant in the ID group

	No. of months post-transplant								
Patient no.	*4*	*8*	*12*	*18*	*24*	*30*	*36*	*48*	*54*
CD02*	45	46	48	68	75	50	80	47	15
CD03*	26	45	52	52	52	35	35	3	x
CD11*	55	68	43	33	25	20	15	x	x
CD12*	73	133	86	d	—	—	—	—	—
CD15*	70	47	57	75	5	x	x	x	x
CD17	50	51	70	53	66	x	x	x	x
CD19*	62	52	59	55	52	x	x	x	x
CD21*	57	30	38	30	x	x	x	x	x
CD22	70	58	57	84	x	x	x	x	x
CD25*	54	50	5	f	—	—	—	—	—
CD28	66	58	57	56	x	x	x	x	x
CD29	63	70	60	x	x	x	x	x	x

*Patients who developed proteinuria of 0.5 g. or more per day during their post-transplant course.
x Insufficient time elapsed since transplantation.
d Death of the patient without transplant failure.
f Failure of the transplant without death of the patient.

TABLE IV.—Comparison of creatinine clearance in ID and NID groups

		Creatinine clearance (ml./min.)				
		ID group		*NID group*		
No. of months post-transplant	*No. of patients*	*Mean*	*Range*	*No. of patients*	*Mean*	*Range*
4	12	58	(26- 73)	4	73	(62- 86)
8	12	59	(30-133)	4	85	(63-102)
12	12	53	(5- 86)	4	76	(58- 91)
18	9	56	(30- 84)	3	86	(72-102)
24	6	46	(5- 75)	3	79	(70- 80)
30	3	35	(20- 50)	2	73	(70- 75)
36	3	43	(15- 80)	1	75	(75)
48	2	25	(3- 47)	—	—	—

Number of patients progressively diminishes with the passage of time for the reasons detailed in Tables I, II and III.

Of the five patients, two had clearly non-immune disease—polycystic kidney disease. More than one year after the original biopsy both patients had nearly doubled their creatinine clearances, although one patient apparently still had proteinuria. Rejection must be implicated, but it was reversible. A comparable improvement did not occur in any of the 22 patients whose original disease was glomerulonephritis. In fact, the majority of these patients went on to progressive deterioration. This alone would suggest that recurrence of original disease played a significant role in their series.

The three remaining patients had "chronic pyelonephritis". The transplanted kidney in two showed progressive decline and retained its status quo in the third. There is increasing evidence that progressive renal destruction can occur with non-obstructive "chronic pyelonephritis" in the absence of bacteria.[13] It may be the end-point of a variety of etiological processes,[14] primary immunological factors not being inconceivable. It is speculative, but possible, that pretransplant immunological factors may have played a role in the deterioration of the transplant in these patients, and we do not believe it is justifiable to include this disease entity in a non-immunological group at this time.

Furthermore, in a more recent series of 15 patients who have survived for longer than one year, the only patient with polycystic disease is free of significant proteinuria while 12 of the remaining patients show this disturbance.[3, 15]

In our own series light microscopy of specimens from the patients with original immune disease has shown progressive glomerular destruction and in several cases the changes were very similar to those of the original disease. The two patients with non-immune original disease, who died of non-renal causes at 12 and 30 months, had no evidence of glomerular pathology on light microscopy.

Further clarification of the problem could be obtained if the histocompatibility of the donor and host were known. Unfortunately we do not have this information. However, it would be unusual that by chance the patients in the ID group would have poor matches and the patients in the NID group would have close matches. Indirect evidence also suggests that this did not occur. Two of the patients in the NID group who are now at 24 and 36 months had severe early rejection reactions and this suggests poor histocompatibility.[1]

In conclusion, it has been our purpose to redirect attention to the importance of the nature of the original disease as a factor in the eventual outcome of cadaveric renal transplantation. It has not been our intention to relegate rejection to a secondary role, nor do we question the importance of histocompatibility studies. In fact, if our observations are correct and recurrence of original immune disease plays a significant role in late failure, the importance of tissue typing is increased. As typing techniques improve, the management of recurrent disease will undoubtedly prove to be a greater obstacle than rejection. Furthermore, recurrent disease may account for the discrepancies reported in the living related donor[16] and the unrelated and cadaveric donor series[4, 17] where close matches have failed and poor matches have succeeded.

Résumé

Echec tardif des homéogreffes de rein de cadavre

Cet article passe en revue les cas de 16 malades ayant subi une greffe de rein de cadavre et qui ont survécu une année au moins. Ces cas sont analysés aux points de vue de la fréquence, de l'importance et de l'évolution de la protéinurie par rapport à la fonction rénale et à la nature de la pathologie originelle.

Il en ressort que la protéinurie évolue progressivement et qu'elle s'accompagne d'un déclin de la fonction rénale quand la maladie primaire est de nature immunitaire. Il n'en est pas ainsi quand la maladie originelle n'est pas de cette nature.

Ces constatations permettent de croire que le retour offensif de la maladie primaire joue un rôle important dans la détérioration tardive des homéogreffes de rein de cadavre.

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